Dimensions of interoception predict premonitory urges and tic severity in Tourette syndrome

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Abstract (150 words)

Interoceptive processes in Tourette syndrome may foster the premonitory urges that commonly precede tics. Twenty-one adults with TS and 22 controls completed heartbeat tracking and discrimination tasks. Three dimensions of interoception were examined: objective accuracy, metacognitive awareness, and subjective (self-report) sensibility. Trait interoceptive prediction error was calculated as the discrepancy between accuracy and sensibility. Participants with TS had numerically lower interoceptive accuracy on the heartbeat tracking task, and increased self-reported interoceptive sensibility. While these group differences were not significant, the discrepancy between lower interoceptive accuracy and heightened sensibility, i.e. the trait interoceptive prediction error, was significantly greater in TS compared to controls. This suggests a heightened higher-order sensitivity to bodily sensations in TS, relative to a noisier perceptual representation of afferent bodily signals. Moreover, interoceptive sensibility predicted the severity of premonitory sensations and tics. This suggests interventions that work to align dimensions of interoceptive experience in TS hold therapeutic potential.

Keywords: body perception; heartbeat; hyperkinetic movement disorder; trait interoceptive prediction error; metacognition

1. Introduction

Tourette syndrome (TS) is a neurodevelopmental hyperkinetic movement disorder characterised by tics, brief repetitive, recurrent movements and vocalisations, experienced as compulsive and 'unvoluntary' (2013). Tics are commonly preceded by 'premonitory' sensations, feelings of discomfort, itch or pressure, which are relieved upon tic release (Cavanna et al., 2017). Premonitory sensations represent a likely causal trigger in tic production, generating a compulsive urge to move in order to relieve uncomfortable bodily feelings (Conceicao et al., 2017; Rae, Critchley, et al., 2018). Here, we investigated this sensory dimension of TS, testing how alterations in the perception of internal bodily signals may contribute to symptom expression.

Premonitory sensations can be explicitly somatosensory, but often are poorly-localisable internal urges motivating movement (Cavanna et al., 2017). Interoception refers to the processing of internal bodily signals, including heartbeats, encompassing afferent signalling, central processing, neural and mental representation of internal bodily signals and the feeling states that they engender (Critchley and Garfinkel, 2017). Interoceptive signals are processed along afferent neural pathways from peripheral nerves to insular cortex, via a thalamic relay, delivering rapid communication to the cortex on bodily state, which is further processed in regions such as anterior cingulate cortex to engender motivational affective behaviours (Craig, 2002; Critchley, 2005; Critchley and Harrison, 2013).

People vary in their sensitivity to internal bodily sensations and this variation is associated with differences in emotional and motivational behaviour, including vulnerability to anxiety or stress disorders (Dunn et al., 2010). Several studies indicate that anxiety is associated with enhanced interoceptive sensibility, reflected by a tendency for people with anxiety to believe that they are interoceptively proficient, as indexed via self-report (Ehlers and Breuer, 1992; Naring and van der Staak, 1995). Enhanced interoceptive accuracy is also reported among

anxiety patients (Dunn et al., 2010). However, a straightforward relationship between interoception and anxiety is challenged by a number of studies that either do not show a relationship between anxiety and interoceptive accuracy (Anthony et al., 1995; Barsky et al., 1994), or reveal a reverse relationship, with reduced interoceptive accuracy related to heightened anxiety (Depascalis et al., 1984). Furthermore, in the heterogeneous 'TS+' spectrum (Robertson and Eapen, 2014), prevalence estimates of comorbid anxiety disorders are 15-40% (Robertson, 2015), suggesting that vulnerability to anxiety may be only one potential element in the consequences of altered interoception in Tourette syndrome.

Individual differences in insular structure and function predict ability to detect internal bodily sensations such as heartbeats (Critchley et al., 2004). In TS, insular grey matter thickness is reduced, $GABA_A$ receptor binding is decreased (Lerner et al., 2012), and furthermore, insular volume reduction, and the strength of functional coupling between the insula and supplementary motor area in both resting-state and task fMRI predict severity of premonitory sensations (Draper et al., 2016; Rae, Polyanska, et al., 2018; Tinaz et al., 2015). Together, these findings indicate a role for insular dysfunction and body perception in the expression of symptoms in TS (Cavanna et al., 2017; Conceicao et al., 2017; Rae, Critchley, et al., 2018), motivating examination of interoceptive function in this condition.

Individual differences in interoception can be quantified using self-report (questionnaire) measures or, more objectively, from performance accuracy on interoceptive tasks, commonly of heartbeat detection. In one previous examination of interoceptive ability, people with TS showed lower accuracy than controls on a heartbeat detection task (Ganos et al., 2015). People with TS also self-report heightened sensitivity to bodily sensations, for example in response to questions such as, "I can often feel my heart beating" (Eddy et al., 2014). This suggests that people with TS may have less precise, yet more intrusive, representations of internal bodily signals; reflected in a mismatch between objective and subjective dimensions of interoception.

Interoception can be conceptualised along three dissociable dimensions, of objective interoceptive *accuracy* (measured from performance on interoceptive tasks); subjective interoceptive *sensibility* (measured from self-report scales); and metacognitive interoceptive *awareness* (insight into interoceptive ability, reflecting correspondence between subjective and objective measures) (Garfinkel et al., 2015). Discrepancy between objective and subjective dimensions of interoception can underlie the expression of clinical symptoms. In high-functioning individuals with autism (another neurodevelopmental condition that can overlap with TS), subjective sensitivity to bodily sensations is typically reported as greater than controls, while performance on objective interoceptive tests such as heartbeat tracking tasks is lower (Garfinkel et al., 2016). This discrepancy, conceptualised as *trait interoceptive prediction error*, predicts the expression of anxiety symptoms and other affective features of autism (Garfinkel et al., 2016). The one previous study in TS found that individuals performed less accurately than controls on a heartbeat tracking task, and furthermore that interoceptive accuracy predicted severity of premonitory sensations (Ganos et al., 2015). Nevertheless, it remains to be established how symptom severity relates to discrete interoceptive dimensions, and trait interoceptive prediction error, i.e. discrepancy between subjective and objective dimensions of interoception.

Interoceptive tests of heartbeat perception also vary in design: Heartbeat tracking tasks (Schandry, 1981) are potentially subject to confounds of time estimation and higher order knowledge of heartrate (Brener and Ring, 2016; Ring and Brener, 1996). Alternatively, heartbeat discrimination tasks, in which participants indicate whether external visual or auditory stimuli are synchronous with their heartbeat, are often harder to implement and test integration of interoceptive with exteroceptive information (Katkin et al., 1983; Whitehead et al., 1977). The heartbeat tracking task can provide a normative spread across samples, while the heartbeat detection task often shows a bimodal distribution of interoceptive performance in which a majority of individuals perform at chance (Garfinkel et al., 2017). These methods thus vary in the different processes they assess, as reflected by both overlapping and distinct

neural substrates, and therefore represent complementary approaches to investigating interoceptive ability (Garfinkel et al., 2015; A. Schulz et al., 2013; S. M. Schulz, 2016).

Here, we tested adults with TS and controls on both heartbeat tracking and discrimination tasks, incorporating trial-by-trial measures of subjective confidence, in order to calculate both interoceptive accuracy, and interoceptive awareness as a metacognitive index. In addition, we recorded general subjective sensitivity to bodily sensations (interoceptive sensibility) using self-report scores on the Body Perception Questionnaire (Porges, 1993). We hypothesised that patients with TS will manifest differences from controls in these dimensions of interoception, including mismatch reflected in trait interoceptive prediction error (as assessed by 2-tailed tests), and that these differences may predict severity of premonitory sensations and tics (according to correlational analyses).

2. Methods

2.1 Participants

Twenty-one adults with TS (12 male; age 18 to 51 yrs, mean 34 yrs; mean years of education 15 yrs) and twenty-two matched controls with no history of neurological or psychiatric disorder (12 male; age 19 to 55 yrs, mean 34 yrs; mean years of education 15 yrs) gave written informed consent to participate. TS participants had received a diagnosis from a UK neurologist or neuropsychiatrist. The two common comorbidities, attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD), were not exclusion criteria, but were noted. Furthermore, presence of anxiety disorder was not an exclusion criteria, but was noted for Generalised Anxiety Disorder (GAD), and social phobia). Six TS participants were taking serotonergic medications, two were taking dopaminergic, and one was taking both serotonergic and dopaminergic medications. The remaining twelve were unmedicated.

Severity of tics, premonitory sensations, ADHD and OCD symptoms were assessed with the Yale Global Tic Severity Scale (YGTSS; tic severity maximum 50, impairment maximum 50); Premonitory Urge for Tics Scale (PUTS; maximum 36); Adult ADHD Self-Report Scale (ASRS; maximum 6); and the Yale Brown Obsessive Compulsive Scale (YBOCS; maximum 40). Self-report anxiety symptoms were assessed with the state ("how you feel right now") and trait ("how you generally feel") versions of the Spielberger Anxiety Inventory (STAI, Spielberger et al., 1983). Demographics and clinical features are listed in Table 1. The study was approved by the National Research Ethics Service South East Coast Brighton Research Ethics Committee.

2.2 Heartbeat tracking task

Participants' heartbeats were monitored using a pulse oximeter attached to their non-dominant index finger ('soft' mount PureLight sensor; Nonin Medical Inc., MN, USA). Participants were instructed to "silently count the number of heartbeats you feel from the time you hear 'start' to

when you hear 'stop'", on six trials of varying duration (25, 30, 35, 40, 45, 50s), presented in a randomised order (Schandry, 1981). Following each trial, participants gave a confidence rating in their perceived number of heartbeats on a visual analogue scale, from 'total guess (no heartbeat awareness)' to 'complete confidence (full perception of heartbeat)', scored from 0 (no heartbeat awareness) to 10 (full perception of heartbeat).

2.3 Heartbeat discrimination task

A series of ten auditory tones (440Hz, 100ms) were delivered synchronously or asynchronously to the participant's heartbeat (Katkin et al., 1983; Whitehead et al., 1977). Synchronous tones were delivered 250ms following the R-wave, adjusting for the average delay (~250ms) between the R-wave and arrival of the pulse at the finger (Payne et al., 2006). Asynchronous tones were delivered with an additional 300ms delay, namely 550ms following R-wave. Following each trial, participants were asked to indicate whether they perceived the tones to be synchronous or asynchronous with their heartbeats, and give a confidence rating in this report using the same visual analogue scale as the heartbeat tracking task. Twenty trials were completed (10 synchronous, 10 asynchronous). The heartbeat discrimination task was run following the heartbeat tracking task to prevent timing of the tones providing cues to participants' heart rate.

2.4 Interoceptive accuracy

Interoceptive accuracy, reflecting objective interoceptive performance, was calculated on the heartbeat tracking task according to the trial-by-trial ratio of perceived to actual heartbeats (1 – ($nbeats_{real}$ - $nbeats_{reported}$) / ($nbeats_{real}$ + $nbeats_{reported}$) / 2) (Garfinkel et al., 2015; Hart et al., 2013). These ratios were averaged to give a mean heartbeat tracking score. On the heartbeat discrimination task, interoceptive accuracy was calculated as the ratio of correct to incorrect synchronicity judgements (range: 0 to 1).

2.5 Interoceptive awareness

Interoceptive awareness, reflecting metacognitive insight into own performance, was calculated on the heartbeat tracking task as the Pearson correlation (SPSS, version 24) between interoceptive accuracy and confidence rating on each trial. Interoceptive awareness on the heartbeat discrimination task was calculated according to the area under the curve using a receiver operating characteristic (ROC) analysis of the trial-by-trial correspondence between accuracy (synchronicity judgement correct / incorrect) and confidence rating (Garfinkel et al., 2015).

2.6 Interoceptive sensibility

Subjective interoceptive sensibility, reflecting self-reported sensitivity to bodily sensations, was calculated as the mean score on the awareness section of the Body Perception Questionnaire (BPQ) (range: 0 to 4) (Porges, 1993).

2.7 Trait interoceptive prediction error

For both the tracking and discrimination tasks, accuracy scores were converted to standardised *z*-values (SSPS), as were the interoceptive sensibility scores from the BPQ. Trait interoceptive prediction error (tIPE) was calculated as the discrepancy between *z*-scored accuracy and sensibility (sensibility – accuracy), for both tracking and discrimination scores. Positive tIPE values reflect a tendency for the individual to *over-estimate* interoceptive ability, while negative values reflect a tendency to *under-estimate* (Garfinkel et al., 2016).

2.8 Statistical analyses

Group differences in interoceptive accuracy and awareness on the tracking and discrimination tasks, and interoceptive sensibility according to BPQ scores, were analysed using independent *t*-tests (SPSS). Furthermore, group differences in tIPE on the heartbeat tracking task ($tIPE_T$) and heartbeat discrimination task ($tIPE_D$) were analysed using two independent *t*-tests. For the comparison of interoceptive accuracy on the tracking task, Levene's test

indicated the distributions of accuracy were significantly different between the two groups (F=6.054, p=0.018), and so we report a Mann-Whitney test (SPSS) for this comparison. We also tested whether TS participants and controls differed significantly from chance performance (0.5) on the discrimination task with two one-sample *t*-tests.

We tested whether interoception related to symptom severity across the TS participants, using a series of 1-tailed Pearson correlations (SPSS) for relationships between the following measures of interoception: (1) accuracy (tracking), (2) accuracy (discrimination), (3) awareness (tracking), (4) awareness (discrimination), (5) sensibility (BPQ), (6) $tIPE_T$, and (7) $tIPE_D$, with tic severity (YGTSS), impairment (YGTSS) and premonitory sensations (PUTS). Given we tested for correlations between a clinical score and several measures of interoception, for each clinical score, we corrected for multiple comparisons using false discovery rate (FDR) across the seven interoceptive indices, in Matlab (Nantick 2013a) using a script by A. Winkler (https://s3.us-east-2.amazonaws.com/brainder/2011/fdr/fdr.m described at https://brainder.org/2011/09/05/fdr-corrected-fdr-adjusted-p-values/) (Benjamini and Hochberg, 1995). We report both FDR corrected and uncorrected p values (Table 2). In addition, we performed two further 1-tailed Pearson correlations, between $tIPE_T$, and (i) state and (ii) trait anxiety (STAI), to examine the association between anxiety and trait interoceptive prediction error, as Garfinkel et al (2016) did in relation to autism spectrum conditions.

2.9 Data availability

The data supporting the results of this study are available at https://psyarxiv.com/pdhqy/ [upon acceptance following peer review].

3. Results

3.1 Interoceptive accuracy

Participants with TS performed the heartbeat tracking task with reduced mean accuracy (0.62), compared to controls (0.75), in line with the findings of Ganos et al (2015) (Figure 1a). However, this difference did not attain threshold significance (U=167.5, p=0.123). There was no significant difference in interoceptive accuracy on the heartbeat discrimination task between participants with TS (0.56) and controls (0.54) (t(41)=0.403, p=0.689). Neither the TS participants (t(20)=1.747, p=0.096), nor the matched controls (t(21)=1.750, p=0.095) differed significantly from chance performance (0.5) on this task.

3.2 Interoceptive awareness

There were no significant differences in metacognitive interoceptive awareness between participants with TS and controls, on the heartbeat tracking task (t(41)=-0.018, p=0.986; TS: 0.261, controls: 0.264) nor the heartbeat discrimination task (t(41)=0.805, p=0.425; TS: 0.568, controls: 0.533).

3.3 Interoceptive sensibility

Participants with TS demonstrated greater mean interoceptive sensibility (2.49) than controls (1.97) on BPQ score, although this difference did not attain threshold significance (t(41)=1.846, p=0.072) (Figure 1b).

3.4 Trait interoceptive prediction error

tIPE reflects the discrepancy between interoceptive accuracy and sensibility (z-scored sensibility minus z-scored accuracy). tIPE on the heartbeat tracking task ($tIPE_T$) was significantly greater in participants with TS (0.58) than controls (-0.53) (t(41)=2.975, p=0.005), reflecting a tendency for participants with TS to be *over-sensitive* to their bodily sensations, and a relative tendency for controls to be *under-sensitive* to such sensations (Figure 1c). This

relative tendency reflects the comparative difference between participants with TS and controls within the present dataset, rather than assuming a fundamental 'ideal' value per se. tIPE on the heartbeat discrimination task ($tIPE_D$), though numerically elevated in participants with TS (0.24), was not significantly different to controls (-0.19) ($t(41)=1.107$, $p=0.275$).

3.5 Impact of interoception on symptom expression

A series of Pearson correlations in the TS group tested for relationships between all measures of interoception and three clinical scores: tic severity (YGTSS), impairment (YGTSS) and premonitory sensations (PUTS). We corrected for multiple comparisons using false discovery rate (FDR), and report both FDR corrected and uncorrected p values (Table 2).

Without FDR correction, interoceptive accuracy (discrimination task) correlated positively with tic severity on the YGTSS ($r=0.375$, $p=0.049$). Interoceptive awareness (tracking task) correlated negatively with the YGTSS impairment score ($r=-0.371$, $p=0.047$). Furthermore, greater interoceptive sensibility predicted severity of all three clinical scores: tic severity ($r=0.518$, $p=0.008$), impairment ($r=0.431$, $p=0.026$), and premonitory sensations ($r=0.571$, $p=0.003$). Even following FDR correction, interoceptive sensibility correlated with the severity of premonitory sensations ($r=0.571$, $p=0.021$) (Figure 2).

The two (1-tailed) correlation tests between $tIPE_T$ and anxiety were not significant, for (i) state ($r = 0.164$, $p = 0.238$) and (ii) trait ($r = 0.273$ $p = 0.115$) anxiety (STAI).

4. Discussion

Interoception describes the central processing of internal bodily signals, including visceral states of arousal, through to their perception as emotional and motivational feelings (Critchley and Garfinkel, 2017). Interoceptive abilities can be defined according to complementary dimensions of objective accuracy, subjective sensibility and metacognitive awareness (Garfinkel et al., 2015). Our findings indicate that, in TS, interoceptive accuracy is numerically reduced, while subjective sensibility, according to self-reported sensitivity to bodily sensations, is numerically increased, although these do not reach statistical significance compared to the control group. Moreover, these interoceptive dimensions interact such that compared to controls, trait interoceptive prediction error, which calculates the discrepancy between accuracy and sensibility, is significantly increased in TS. Thus, TS participants *over-estimate* their interoceptive ability or are *over-sensitive* to bodily sensations, relative to the precision with which they can detect them. In contrast, controls show *under-estimation* and *relative insensitivity* to such signals. Furthermore, when examining the relation between dimensions of interoception and symptom severity in individuals with TS, heightened general sensitivity to bodily sensations was found to be a strong predictor of the severity of premonitory sensations, such that the greater the ratings of interoceptive sensibility, the worse their experience of premonitory sensations that can trigger tics. These results provide direct evidence linking the often-overlooked sensory symptoms of TS to general aspects of self-representation that are built as expectations over time from bodily feeling states and their integration across organ systems (Rae, Critchley, et al., 2018).

Interoceptive information concerning the physiological arousal and integrity of the body is processed through afferent pathways to representations within insula cortex (Critchley and Garfinkel, 2017). In TS, insular grey matter thickness is reduced, and this reduction correlates with severity of premonitory sensations (Draper et al., 2016). Furthermore, the strength of functional connectivity between the right dorsal insula and SMA also predicts severity of

premonitory sensations (Tinaz et al., 2015), implying that insular dysfunction and the associated representation, integration and perception of afferent bodily signals underpins the expression of sensorimotor symptoms in TS. The functional corollary of these neuroanatomical findings is that individuals with TS would show differences in aspects of interoception compared to controls, and that the nature of such differences will provide further insight into symptom genesis. Indeed, the one previous study on interoception in TS, which focused purely on the dimension of interoceptive accuracy using the heartbeat tracking task, reported poorer interoceptive performance in TS, which was associated with premonitory sensation severity (Ganos et al., 2015).

In line with that previous result, we found that numerically, participants with TS had lower interoceptive accuracy on the same task. Our results did not attain threshold statistical significance, which likely reflects the limitation of patient sample sizes within our (n=21) and the earlier (n=19) studies (Ganos et al., 2015); relative to the normative distribution of heartbeat tracking accuracy. However, it is noteworthy that both sets of findings are broadly consistent, not only in direction of the effect, but in the observed performance levels within the TS (0.62 vs 0.58) groups, suggesting that there is a moderate reduction in interoceptive accuracy in TS.

While the heartbeat tracking task offers advantages for investigating interoception in clinical groups, being straightforward to administer, one drawback is that participants may estimate passage of time, rather than attend as instructed to their heartbeats, and report instead their perception of elapsed seconds as a proxy measure for the number of beats (Ring and Brener, 1996). We therefore also administered a heartbeat discrimination task, in which participants indicate whether tones are delivered synchronously or asynchronously to the heartbeat, as this task is not subject to the same concern. Furthermore, heartbeat tracking and discrimination tasks likely test complementary facets of interoceptive function (Garfinkel et al., 2015; Ring and Brener, 2018), engaging different functional brain circuits (S. M. Schulz, 2016),

and differentially modulated by stressors (A. Schulz et al., 2013) or neuropeptides (Betka et al., 2018). Participants with TS did not show altered interoceptive accuracy on the discrimination task compared to controls. However, floor effects on heartbeat discrimination tasks are well-described, particularly within small samples (Garfinkel et al., 2015; Khalsa et al., 2009). Accuracy on the heartbeat discrimination task also typically follows a bimodal distribution with relatively few people performing with high accuracy. This can limit the usefulness of comparisons between clinical and control samples, since both groups may be at chance performance (Garfinkel et al., 2016). Indeed, this was found to be the case in our study: the mean score of both the TS participants (0.56) and controls (0.54) was not significantly different from chance (0.5). An alternative approach is to quantify, and then to control for, the time estimation aspect of the heartbeat tracking task. Participants are asked to report perceived time intervals, separately to perceived heartbeats, for trial lengths matched in time to those used within the heartbeat tracking task. Time estimation ability can then be added as a covariate in subsequent analyses (Murphy et al., 2018). However, the estimation of time intervals may in part rely on interoceptive processing (Craig, 2009; Wittman, 2016). This represents a valuable future avenue for studies of interoception in TS.

In addition to the dimension of interoceptive accuracy, we characterised experiential and metacognitive aspects of interoception: Participants completed self-report questionnaires of their subjective sensitivity to bodily sensations, and also rated confidence in their interoceptive judgements. This enabled the calculation of interoceptive awareness (insight), a metacognitive reflection on participants' own interoceptive accuracy. It is noteworthy that for both the tracking and discrimination tasks, interoceptive awareness was equivalent in both participants with TS and controls. This suggests that people with TS are unimpaired in short-term metacognitive capacity to judge their own objective interoceptive performance on a trial-by-trial basis, adjusting confidence based on the relative accuracy of each judgement**.** However, this measure was based upon within participant correlations of confidence-accuracy judgements, utilising only a limited number of data-points (n=6), and thus may not be sufficiently stable

within participants to then detect between group differences. The use of larger numbers of trials in future heartbeat tracking studies will increase the stability of confidence-accuracy judgement correlations as a metacognitive index.

Objective measures of interoception rely not only on appropriate sampling in task design, but also in application of suitable hardware to sample physiology. We used a soft finger sensor, rather than spring-loaded finger clips, so as to minimise the possibility for sensation of the heartbeat via pressure from the sensor. However, one cannot discount that participants engage in covert strategies to exert pressure and gain a sensory cue to their heartbeat perception. Use of sensors with which participants could not covertly exert pressure, such as via ear clips, may assist in ensuring such confounds are minimised.

Compared to objective measures of interoception, a different picture emerges in TS with subjective self-reported sensitivity to bodily sensations. Compared to controls, participants with TS report numerically increased sensitivity to bodily sensations, according to scores on the Body Perception Questionnaire (Porges, 1993). This instrument accesses more general information concerning the perception of bodily sensations, integrated over time and across channels; scoring, for example, how frequently one experiences palms sweating, rapid breathing, and increased heart rate. The TS population scored higher on average than controls, though this effect did not reach significance (reflecting group sizes and high within-group heterogeneity). However, when compared to heartbeat tracking performance (by calculating the *trait interoceptive prediction error*), TS participants differed significantly from controls. We have conceptualised the computed relationship between this broad measure of subjective sensitivity to bodily sensations and objective performance accuracy on interoceptive tasks as *trait interoceptive prediction error* (Garfinkel et al., 2016). This indexes discrepancy between detection of interoceptive signals and reportable self-beliefs or expectations concerning bodily perception. The prediction and appraisal of internal bodily sensations (against expectations) can underpin emotional experience, motivated behaviour

and even self-representation (Barrett and Simmons, 2015; Seth and Friston, 2016). Speculatively, our data suggests that the balance between higher-order subjective representation of bodily sensation and the veracity of ascending bodily signalling might be critical to sensory triggering of tics (Rae, Critchley, et al., 2018). In particular, 'sensory surprise' (which may be indicated by interoceptive sensibility), represented in the anterior insula, may trigger onward signals to cortical motor preparation areas, namely the supplementary motor area, for mitigating action, and do so in proportion to strength of premonitory sensations or urges (Rae, Critchley, et al., 2018).

Our findings extend a previous examination of subjective bodily awareness in individuals with TS, who reported greater sensitivity to internal bodily sensations on the Private Body Consciousness Scale (Eddy et al., 2014). By examining three dimensions of interoception within the same sample, we can relate subjective experience to objective performance to shed light on how interoceptive experience aligns across these axes. It is plausible that the trait interoceptive prediction error identified here, reflecting a discrepancy between an inaccurate central processing of bodily signals, and heightened subjective autonomic experiences, generates 'sensory surprise' in people with TS. In probabilistic hierarchical models of brain function, such mismatches of bodily signals and subjective experience within the insular cortex may engender premonitory sensations, as unexpected sensory symptoms that require mitigating action to remove, generating tics (Rae, Critchley, et al., 2018).

Our observation that interoceptive sensibility correlated positively with severity of premonitory sensations, as measured by the Premonitory Urge for Tics Scale (PUTS) (Woods et al., 2005), provides further support for this putative mechanism, such that the greater a patient's subjective self-report sensitivity, the worse the premonitory sensations. We note, however, that while approximately 60% of tics (in one report) are experienced as preceded by premonitory experiences (Leckman et al., 1993), not all tics are associated with premonitions, and indeed, a small minority of people with TS report rarely feeling premonitory sensations or

urges at all. Thus, while we observed a correlation between premonitory sensation severity and interoceptive sensibility, sensitivity to subjective bodily perception cannot directly represent a causal determination of tics in all individuals with TS. It is interesting that it was the interoceptive sensibility measure that predicted symptom severity, rather than trait interoceptive prediction error. This may relate to the contribution to the trait interoception prediction error score of participants' heartbeat tracking accuracy, which, though numerically lower, was not significantly different to controls. Nevertheless, these findings require further validation in larger numbers of people with TS, which would also permit examination of interoception in people with TS who report substantial premonitory experiences versus those who do not.

In addition to validation analyses, larger samples may permit examination of effects of comorbidity and medication status, with TS characterised by significant heterogeneity along the 'pure TS / TS+ / full blown TS' spectrum (Robertson and Eapen, 2014). This may be particularly important in light of findings that OCD patients without tics have increased interoceptive accuracy, but lower subjective confidence (Yoris et al., 2017). Beyond the cardinal comorbidities of ADHD and OCD, it will be useful to examine whether an association between interoception and anxiety in autistic spectrum conditions (Garfinkel et al., 2016; Palser et al., 2018) is present in individuals who have comorbid tics, and furthermore whether subsamples of people with TS with varied anxiety diagnoses differ in interoceptive abilities. For example, some may meet criteria for GAD, and some for social phobia, while others may not meet diagnostic criteria for anxiety disorders, or self-report significant anxiety above that of control samples. Effects of medication are also important to consider, with a variety of dopaminergic, noradrenergic, and serotonergic medicines (amongst others) given either as a frontline treatment for tics, or to treat comorbidities such as ADHD and OCD, with these monoamine systems likely to modulate activity in interoceptive pathways (Critchley and Garfinkel, 2016).

The association between severity of premonitory sensations and subjective sensitivity to bodily sensations highlights the potential for therapeutic strategies in TS that target autonomic control of internal bodily state and its feedback into conscious awareness of interoceptive feelings. For example, biofeedback training enables patients to manage autonomic reactivity through focused attention: However, typical training protocols may need to be tailored to avoid confounding occurrence of tics themselves, which can interrupt physiological feedback (Nagai et al., 2014). Alternatively, reports from patients suggest that premonitory sensations can be used as cues for countermeasures and voluntary suppression of tics (Bliss, 1980; Kwak et al., 2003; Leckman et al., 1993). Indeed, the current mainstay behavioural treatments for tics, such as Habit Reversal Therapy and Cognitive Behavioural Intervention for Tics, make use of awareness of urges as a core component of the therapeutic approach (Woods et al., 2008). Our results suggest that patients who report the greatest subjective sensitivity to bodily sensations may be the best empowered to use premonitory symptoms to manage the expression of tics if desired. However, there is limited empirical evidence to date suggesting an association between severity of premonitory sensations and tic suppression success outside a therapeutic program (Ganos et al., 2012).

Some evidence suggests that interoceptive abilities can be increased through dedicated training programmes (Bornemann et al., 2014). It is plausible therefore that, by enhancing interoceptive accuracy in TS, subjective bodily sensations may become less potent, by aligning expected sensations with perceived sensations. This holds promise for reducing premonitory sensations in TS, and thereby, potentially fostering a reduction in tics.

4.1 Conclusions

Experiential aspects of interoception are altered in TS, contributing to the reported severity of premonitory sensations. A decrease in interoceptive accuracy relative to an increased interoceptive sensibility is reflected in a trait interoceptive prediction error in TS individuals that impacts the appraisal of and reaction to interoceptive cues, yet metacognitive insight into

interoception task performance, however, is no different to controls. A heightened subjective sensitivity to bodily sensations predicts the severity of premonitory sensations, which suggests that interventions that work to align dimensions of interoceptive experience in TS hold therapeutic potential.

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Figures

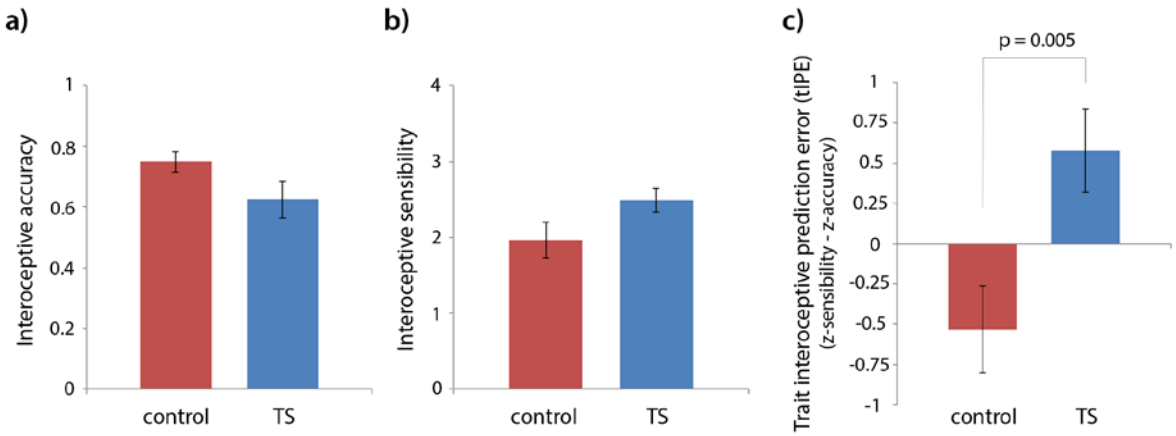

Figure 1. a) Interoceptive accuracy on the heartbeat tracking task is numerically lower in participants with TS, while b) interoceptive sensibility according to the Body Perception Questionnaire is numerically higher (although the differences are not significant at $p<0.05$). c) This discrepancy is reflected in a significantly greater trait interoceptive prediction error (tIPE).

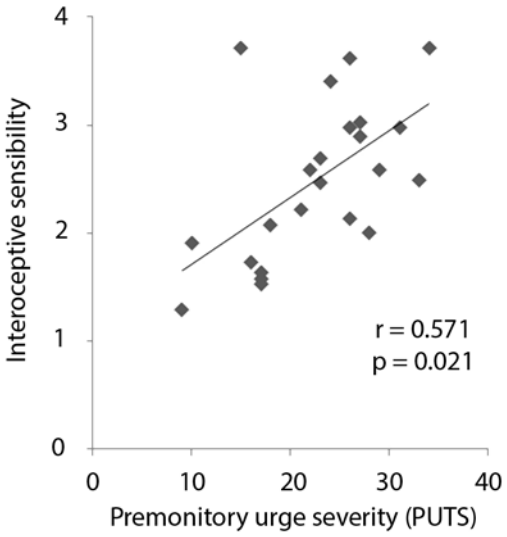

Figure 2. In TS participants, greater interoceptive sensibility, according to the Body Perception Questionnaire, predicts the severity of premonitory sensations (p=0.003, p=0.021 following FDR correction).

Table 1. Demographic and clinical features of participants, given as mean (range).

	Tourette syndrome (*n*=21)	**Controls** (*n*=22)
Male / female	12 / 9	12 / 10
Age	34 (18 – 51)	34 (19 – 55)
Years of education	15 (11 – 17)	15 (11 – 17)
YGTSS: tic severity	26 (6 – 44)	-
YGTSS: impairment	19 (0 – 50)	-
YGTSS: total	45 (6 – 84)	-
PUTS	23 (9 – 34)	-
ASRS	4 (0 – 6)	1 (0 – 4)
YBOCS	16 (0 – 32)	6 (0 – 20)
Spielberger State Anxiety Inventory	41 (22-71)	28 (20-39)
Spielberger Trait Anxiety Inventory	50 (22-68)	34 (23-50)
Diagnosed ADHD	6	-
Diagnosed OCD	9	-
Diagnosed GAD	11	-
Diagnosed social phobia	6	-

YGTSS = Yale Global Tic Severity Scale; PUTS = Premonitory Urge for Tics Scale; ASRS = Adult ADHD Self-Report Scale; YBOCS = Yale Brown Obsessive Compulsive Scale.

Table 2. Correlations (1-tailed) between measures of interoception and tic severity (YGTSS), impairment (YGTSS) and premonitory sensations (PUTS).

	Accuracy tracking	Accuracy discrimination	Awareness tracking	Awareness discrimination	Sensibility	$tIPE_T$	$tIPE_D$
YGTSS tic severity	r=0.258 p=0.129 p_{FDR}=0.217	r=0.375 **p=0.047** p_{FDR}=0.165	r=-0.233 p=0.155 p_{FDR}=0.217	r=-0.251 p=0.136 p_{FDR}=0.217	r=0.518 **p=0.008** p_{FDR}=0.056	r=0.058 p=0.401 p_{FDR}=0.433	r=-0.039 p=0.433 p_{FDR}=0.433
YGTSS impairment	r=0.125 p=0.295 p_{FDR}=0.413	r=0.005 p=0.491 p_{FDR}=0.491	r=-0.371 **p=0.049** p_{FDR}=0.172	r=0.050 p=0.414 p_{FDR}=0.483	r=0.431 **p=0.026** p_{FDR}=0.182	r=0.142 p=0.270 p_{FDR}=0.473	r=0.264 p=0.124 p_{FDR}=0.289
Premonitory sensations (PUTS)	r=0.274 p=0.114 p_{FDR}=0.399	r=0.211 p=0.180 p_{FDR}=0.315	r=-0.242 p=0.145 p_{FDR}=0.338	r=-0.010 p=0.482 p_{FDR}=0.482	r=0.571 **p=0.003** ***p_{FDR}=0.021***	r=0.075 p=0.373 p_{FDR}=0.435	r=0.153 p=0.253 p_{FDR}=0.354

Significant uncorrected correlations (p) indicated in **bold**, significant FDR corrected correlations (p_{FDR}) indicated in ***bold italics***.